REMARKS

With this Amendment, Applicants have amended Claims 26 and 27. After entry of the instant amendment, Claims 1, 3-18, 20-27, 29, 34-35, 37, 42, 44, 54-56. Attached herewith is Exhibit A (Version with Markings to Show Changes Made) and Exhibit B (Pending Claims After Entry of the Instant Amendment).

I. THE AMENDMENT OF THE CLAIMS

Claims 26 and 27 have been amended to correct dependency and a typographical error. Support for amended Claims 26 and 27 may be found, for example, in Claims 26 and 27 as originally filed and in the specification, for example, at page 44, lines 15 to 29.

CONCLUSION

No fees in addition to the fees for additional claims indicated on the fee sheet filed herewith are believed due. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP, U.S. Deposit Account No. 16-1150 (Order No. 9196-022-999). A copy of this sheet is enclosed for accounting purposes.

Respectfully submitted,

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EXHIBIT A

Claim Amendment: Version with Markings to Show Changes Made

26. (Twice amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or [21] 22 in which each HH is independently [a] an altered D-enantiomeric peptide or peptide analogue [according to Claim 3].

27. (Twice amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a deleted D-enantiomeric peptide or peptide analogue [according to Claim 10].

EXHIBIT B

Claim Amendment: Pending Claims After Entry of the Instant Amendment

1. An ApoA-I agonist compound comprising:

(i) a 22 to 29-residue D-enantiomeric peptide or peptide analogue which forms an amphipathic α-helix in the presence of lipids and which comprises formula (I):

$$Z_1\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_7\text{-}X_8\text{-}X_9\text{-}X_{10}\text{-}X_{11}\text{-}X_{12}\text{-}X_{13}\text{-}X_{14}\text{-}X_{15}\text{-}X_{16}\text{-}X_{17}\text{-}X_{18}\text{-}X_{19}\text{-}X_{20}\text{-}X_{21}\text{-}X_{22}\text{-}X_{23}\text{-}Z_2$$

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is D-Ala (a), Gly (G), D-Gln (q), D-Asn (n), D-Asp (d) or D-Pro (p);

X_2 is a D-enantiomeric aliphatic residue;

X_3 is D-Leu (l) or D-Phe (f);

X_4 is a D-enantiomeric acidic residue;

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X_7 is a D-enantiomeric hydrophilic residue;

X_8 is a D-enantiomeric acidic or a basic residue;

X_9 is D-Leu (l) or Gly (G);

X_{10} is D-Leu (l), D-Trp (w) or Gly (G);

X_{11} is a D-enantiomeric hydrophilic residue;

X_{12} is a D-enantiomeric hydrophilic residue;

X_{13} is Gly (G) or a D-enantiomeric aliphatic residue;

X_{14} is D-Leu (l), D-Trp (w), Gly (G) or D-Nal;

X_{15} is a D-enantiomeric hydrophilic residue;

X_{16} is a D-enantiomeric hydrophobic residue;

X_{17} is a D-enantiomeric hydrophobic residue;

X_{18} is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;

X_{19} is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;

X_{20} is a D-enantiomeric basic residue;

X_{21} is a D-enantiomeric aliphatic residue;

X_{22} is a D-enantiomeric basic residue;

X_{23} is absent or a D-enantiomeric basic residue;

Z_1 is R_2N- or RC(O)NR-;

Z_2 is -C(O)NRR, -C(O)OR or -C(O)OH or a salt thereof;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl, 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one or more bonds between residues 1 through 7 are independently a substituted amide, an isostere of an amide or an amide mimetic; and

each " - " between residues X_1 through X_{23} independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 14 to 28-residue deleted D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, X_{21} and X_{22} are optionally deleted; or

(iii) a 22 to 29-residue altered D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one of residues X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, X_{21}, X_{22} or X_{23} is conservatively substituted with another D-enantiomeric residue.

3. The ApoA-I agonist compound of Claim 1 which is the altered D-enantiomeric peptide or peptide analogue according to formula (I).

4. The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophobic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

5. The ApoA-I agonist compound of Claim 4 in which:

X_1 is D-Pro (p), Gly (G) or D-Ala (a);

X_2 is D-Ala (a), D-Leu (l) or D-Val (v);

X_3 is D-Leu (l) or D-Phe (f);

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X_9 is D-Leu (l) or Gly (G);

X_{10} is D-Leu (l), D-Trp (w) or Gly (G);

X_{13} is D-Leu (l), Gly (G) or D-Aib;

X_{14} is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);

X_{16} is D-Ala (a), D-Nal, D-Trp (w), Gly (G), D-Leu (l) or D-Phe (f);

X_{17} is D-Leu (l), Gly (G) or D-Nal;

X_{21} is D-Leu (l); and

at least one of X_4, X_7, X_8, X_{11}, X_{12}, X_{15}, X_{18}, X_{19}, X_{20}, X_{22} and X_{23} is conservatively substituted with another D-enantiomeric residue.

6. The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophilic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

7. The ApoA-I agonist compound of Claim 6 in which:

X_4 is D-Asp (d) or D- Glu (e);

X_7 is D-Lys (k), D-Arg (r) or D-Orn;

X_8 is D-Asp (d) or D-Glu (e);

X_{11} is D-Asn (n) or D-Gln (q);

X_{12} is D-Glu (e) or D-Asp (d);

X_{15} is D-Asp (d) or D-Glu (e);

X_{18} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

X_{19} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

X_{20} is D-Lys (k) or D-Orn;

X_{22} is D-Lys (k) or D-Orn;

X_{23} is absent or D-Lys (k); and

at least one of X_1, X_2, X_3, X_5, X_6, X_9, X_{10}, X_{13}, X_{14}, X_{16}, X_{17} and X_{21} is conservatively substituted with another D-enantiomeric residue.

8. The ApoA-I agonist compound of Claim 7 in which X_3 is D-Leu (l) or D-Phe (f), X_6 is D-Phe (f), X_9 is D-Leu (l) or Gly (G), X_{10} is D-Leu (l) or D-Trp (w) or Gly (G) and at least one of X_1, X_2, X_5, X_{13}, X_{14}, X_{16}, X_{17} and X_{21} is conservatively substituted with another D-enantiomeric residue.

9. The ApoA-I agonist compound of Claim 4 or 6 in which the substituting D-enantiomeric residue is classified within the same sub-category as the substituted D-enantiomeric residue.

10. The ApoA-I agonist compound of Claim 1 which is the deleted D-enantiomeric peptide or peptide analogue according to formula (I).

11. The ApoA-I agonist compound of Claim 10 in which one or two helical turns of the peptide or peptide analogue is optionally deleted.

12. The ApoA-I agonist compound of Claim 1 which is a 22-23 residue D-enantiomeric peptide or peptide analogue according to formula (I).

13. The ApoA-I agonist compound of Claim 12 in which:

the "-" between residues designates -C(O)NH-;

Z_1 is H_2N-; and

Z_2 is -C(O)OH or a salt thereof.

14. The ApoA-I agonist compound of Claim 13, in which:

X_1 is D-Ala (a), Gly (G), D-Asn (n), D-Gln (q), D-Asp (d) or D-Pro (p);

X_2 is D-Ala (a), D-Val (v) or D-Leu (l);

X_3 is D-Leu (l) or D-Phe (f);

X_4 is D-Asp (d) or D-Glu (e);

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X_7 is D-Lys (k), D-Arg (r) or D-Orn;

X_8 is D-Asp (d) or D-Glu (e);

X_9 is D-Leu (l) or Gly (G);

X_{10} is D-Leu (l), D-Trp (w) or Gly (G);

X_{11} is D-Asn (n) or D-Gln (q);

X_{12} is D-Glu (e) or E-Asp (d);

X_{13} is Gly (G), D-Leu (l) or D-Aib;

X_{14} is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);

X_{15} is D-Asp (d) or D-Glu (e);

X_{16} is D-Ala (a), D-Nal, D-Trp (w), D-Leu (l), D-Phe (f) or Gly (G);

X_{17} is Gly (G), D-Leu (l) or D-Nal;

X_{18} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

X_{19} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

X_{20} is D-Lys (k) or D-Orn;

X_{21} is D-Leu (l);

X_{22} is D-Lys (k) or D-Orn; and

X_{23} is absent or D-Lys (k).

15. The ApoA-I agonist compound of Claim 14, in which X_{23} is absent.

16. The ApoA-I agonist compound of Claim 13 or 14, in which one of X_{18} or X_{19} is D-Gln (q) or D-Asn (n) and the other of X_{18} or X_{19} is D-Lys (k) or D-Orn.

17. The ApoA-I agonist compound of Claim 14 in which each of X_9, X_{10}, X_{13}, X_{14}, X_{15} and X_{17} is other than Gly (G).

18. The ApoA-I agonist compound of Claim 14 in which one of X_9, X_{10}, X_{13}, X_{14}, X_{15} and X_{17} is Gly (G) and the others are other than Gly (G).

20. A multimeric ApoA-I agonist compound which comprises formula (II):

(II) $HH\{LL_m\text{-}HH\}_nLL_m\text{-}HH$

or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

each "HH" is independently a peptide or peptide analogue according to Claim 1;

each "LL" is independently a bifunctional linker; and

each " - " independently designates a covalent linkage.

21. A multimeric ApoA-I agonist compound which comprises formula (III):

(III) $X\text{-}N_{ya}\text{-}X_{(ya-1)}\text{-}(\text{-}N_{yb}\text{-}X_{(yb-1)})_p$

or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $HH\text{-}(\text{-}LL_m\text{—}HH\text{-})_nLL_m\text{—}HH$;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

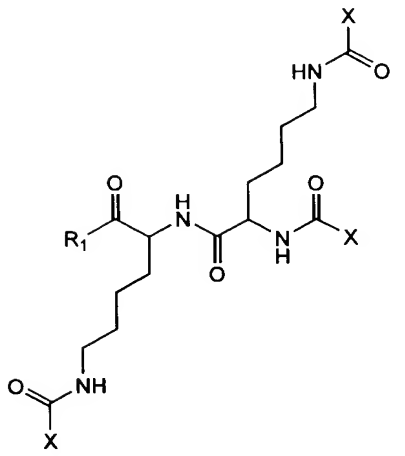
N_{ya} and N_{yb} are each independently a multifunctional linking moiety where y_a and y_b represent the number of functional groups on N_{ya} and N_{yb}, respectively;

each y_a or y_b is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

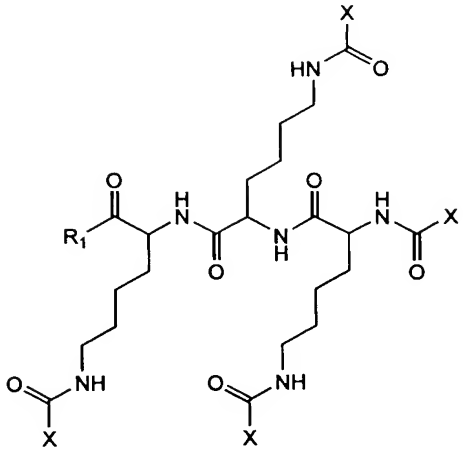
each "—" independently designates a covalent bond.

22. A multimeric ApoA-I agonist compound which comprises formula (IV) or (V):



(IV)

-OR-



(V)

or a pharmaceutically acceptable salt thereof, wherein:

each X is independently HH-(-LL_m—HH-)-$_n LL_m$—HH;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R_1 is -OR or -NRR; and

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl; (C_5-C_{20}) aryl (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl.

23. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which the bifunctional linker is cleavable.

24. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which n is 0.

25. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which m is 0.

26. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently an altered D-enantiomeric peptide or peptide analogue.

27. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a deleted D-enantiomeric peptide or peptide analogue.

29. An ApoA-I agonist-lipid complex comprising an ApoA-I agonist compound and a lipid, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.

34. The ApoA-I agonist-lipid complex of Claim 29 in which the lipid is sphingomyelin.

35. The ApoA-I agonist-lipid complex of Claim 34 which is in the form of a lyophilized powder.

37. A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.

42. The pharmaceutical composition of Claim 37, in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist compound and a lipid.

44. A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

54. A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

55. The method of Claim 44 or 54 in which said subject is a human.

56. The method of Claim 44 or 54 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist is administered to said subject.